REMARKS/ARGUMENTS

The Applicant respectfully requests reconsideration of the present Application in view of the foregoing amendments and in view of the reasons that follow. Claim 1 is currently amended. Claims 24 and 25 are new. Claims 1-5, 7, 9-14, 24 and 25 are now pending in this Application.

I. New Claims

New claim 24 and 25 have been added to further illustrate the preferred range of the present method for an effective amount of the mono-phasic solution of phenol and guanidine isothiocyanate and lysis buffer. Evidence of these ranges are represented in the specification of the patent application, specifically in the examples provided as well as a natural range extrapolated from the examples provided in the specification.

II. Claim Rejections - 35 U.S.C. § 112

Claims 1-5, 7 and 9-14 were rejected under the first and second paragraph of U.S.C. § 112. The Applicant has deleted the term "effective" and replaced it with appropriate ranges that are used in the present application. Therefore, Applicant respectively request the withdrawal of this rejection.

III. Claim Rejections - 35 U.S.C. § 103

A. Obviousness

When determining the question of obviousness, underlying factual questions are presented which include (1) the scope and content of the prior art; (2) the level of ordinary skill in the art at the time of the invention; (3) objective evidence of nonobviousness; and (4) the differences between the prior art and the claimed subject matter. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Moreover, with regard to the last prong of the *Graham* inquiry, "[t]o determine whether there was an apparent reason to combine the known

elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit." KSR International v. Teleflex Inc., 127 U.S. 1727 (2007).

The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986). The level of ordinary skill in the art of computer programming may be determined by looking to the references of record. In re GPAC, Inc., 57 F.3d 1573, 35 USPQ2d 1116 (Fed. Cir. 1995). The references of record in this case reveal that a moderately high level of sophistication in is present in the subject area of the subject area of the instant application. Thus, applicants submit that, as substantiated by the cited references, those with at least a bachelor's degree in biology, microbiology, chemistry and/or the like with some experience a laboratory setting would most likely be a person with ordinary skill in this field of endeavor.

With respect to objective evidence of non-obviousness, the Applicants submit that the record supports the conclusion that there are long-felt but unsolved needs met by the present invention. For at least this reason, the Applicants respectfully submit that the claimed invention is not obvious in view of the cited references.

Finally, prima facie obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references. This motivation-suggestion-teaching test informs the Graham analysis. "To reach a non-hindsight driven conclusion as to whether a

person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references, " there must be "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." In re Kahn, (Fed. Cir. 2006). The *KSR International* decision by the Supreme Court has not eliminated the motivation-suggestion-teaching test to determine whether prior art references have been properly combined. Rather, in addition to the motivation-suggestion-teaching test, the Court discussed that combinations of known technology that are "expected" may not be patentable. Stated in the affirmative, therefore, combinations are non-obvious and patentable if unexpected. In the present application, no single prior art reference nor any combination thereof (legitimate or otherwise) meets the claimed limitations of Applicants' invention.

B. Commercial Success and Long-Felt Need

Applicants are providing evidence by way of a 37 C.F.R. § 1.132 declaration of Dr. Nancy Dohse Hanson (attached hereto) of both the commercial success of the invention of the present application and of an unresolved and long-felt need for the invention. Dr. Hanson's CV is attached to the Declaration as well.

Applicants respectfully submit that the claimed invention, as supported by the attached Declaration under 37 C.F.R. § 1.132, exhibits commercial success directly resulting from after-arising incorporation of the claimed invention. In the present case, the present invention has been licensed and sold under the Invitrogen brand. These sales have been ongoing since 2005. During this timeframe the licensee has had approximately Three Hundred Sixty Thousand Dollars in net profits and paid to Applicant over Eighteen Thousand Dollars in royalties. Claim 1 provides for a specific range of microliters used for the admixture for the method of isolating

RNA from a biological specimen of the present invention. The present invention provides superior results and amounts of RNA. Specifically, this method works well for all types of bacteria. Once the licensee adopted this method of isolating RNA, it has become even more successful. The claimed features of the present invention directly led to this commercial success. A presumption of commercial success exists. Therefore, the after-arising incorporation of the claimed invention into methods directly resulted in commercial success, as evidenced by the attached 37 C.F.R. § 1.132 Declaration and as shown above. Accordingly, it is respectfully submitted that the rejection is overcome and respectfully requested that the rejection be withdrawn.

Applicants respectfully submit that the claimed invention, as supported by the attached Declaration under 37 C.F.R. § 1.132, solves a long-felt need in the industry and succeeds where others have failed. Although there are many different methods for isolating RNA, the RNA isolated was poor in quality, contaminated, was a slow process or all of the above. The methods and compositions of the present invention permit the easy preparation of highly pure RNA samples from clinical isolates with a minimum amount of contaminating genomic DNA. It is clear that a long-felt need arose for isolating RNA in a purer form, in a more economical way and more quickly. Further, others have been unable to solve this need. However, the claimed invention was able to meet this need and succeed where others had failed because of the specific admixture of from about 750 to about 1000 microliters of mono-phasic solution of phenol and guanidine isothiocyanate and from about 100 to about 300 microliters of lysis buffer. Thus, the claimed invention addressed this long-felt need and succeeded where others had failed before, as evidenced by the attached 37 C.F.R. § 1.132 Declaration and as shown above. Accordingly, it is

respectfully submitted that the rejection is overcome and respectfully requested that the rejection be withdrawn.

C. Rejection of Claims 1-5, 7 and 9-14

Claims 1-5, 7 and 9-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cook et al. (J. Clin Microbiol. 2000 Dec.; 38(12):4326-31) in view of Chomcynski (5,345,994) and in further view of Majumdar (Biotechniques. 1991 Jul.; 11(1):94-101). Applicants have amended claim 1 to recite, among other limitations, an admixture of (i) "from about 750 to about 1000 microliters of a mono-phasic solution of phenol and guanidine isothiocyanate, and (ii) from about 100 to about 300 microliters of a lysis buffer under conditions and for a time appropriate to form a homogenate."

The Office Action states, "[w]ith regard to the admixture of solutions (i) and (ii), Cook expressly teaches that the CATRIMOX-TRIZOL method was performed on some [whole blood] samples without the two DEPC water washes. Thus within these methods, a CALITROX residue was present in the reaction vessel during the addition of TRIZOL reagent." (internal citations omitted). Catrimox is a cationic surfactant used for lysing blood cells. Cook states that it added a lysis solution but the specifics of that solution are not given nor are they provided in the articles cited within the methodology when described. As previously pointed out, the prior art of record relates to RNA extraction from whole blood, whereas the present invention is related to RNA extraction from a bacterial sample. With regards to lysing whole blood cells, these types of cells are more fragile than bacterial cells and the hypotonic solution used would not be appropriate for bacterial cells as bacterial cells have a cell wall in addition to one membrane (Gram-positive bacteria) or two membranes for Gram-negatives. It would not have been common practice to assume that the methodology taught by Cook alone or in combination

with the other cited references would work for bacteria. The chemistry of the sample solutions involved and cell structures disclosed in Cook and the present application are completely different. There would be no reason to expect that the application of a method useful for the extraction of RNA from whole blood to an extraction of RNA from a bacterium would be fruitful.

Furthermore, as amended, the claims recite specific ranges of amounts that are used in the present invention. The reliance in the Office Action in making its rejection based on the possible presence of residual amounts of one or more of these components in a prior art extraction of RNA from whole blood is misplaced. The potential presence of a residual amount of a reagent in the extraction of RNA from whole blood is not an enabling disclosure for the use of an effective amount of the reagent in the extraction of RNA from a bacterium. More specifically, the ranges claimed in claim 1 and in new claims 24 and 25 are not provided for or disclosed in the cited prior art.

Majumdar teaches simultaneous RNA and DNA extraction for eukaryotic and bacterial samples. The major difference between the RNA extraction for bacteria of Majumdar and the present application is the detergent in the lysis solution. Majumdar teaches the use of Triton-X and the lysis solution disclosed in the present application uses SDS. Triton-X is a mild detergent whereas SDS is a harsher detergent allowing a more effective method for breakage of the bacterial cells. In many cases clinical bacterial isolates require a harsher lysis procedure due to capsule production and lipopolysaccharide make-up of the different cell types. It is also a concern that Majumdar isolates both DNA and RNA from the same sample. Evaluating RNA expression using this method of RNA isolation would surely provide RNA expression data

contaminated with DNA and thus unusable for the present application. The gels evaluating the ribosomal RNA data are not full-length and, typically, if one has DNA contamination one would be able to visualize that contamination at the top of the gel which Majumdar has neglected to show. In addition, only one species of bacteria is used for analysis in Majumdar. This organism is not a typical laboratory strain or any type of clinical strain found during patient care but is a green photosynthetic bacteria. It is puzzling that this bacteria was chosen and it is not what would typically have been chosen by one in the art to evaluate this type of technique. Therefore, it would not have been obvious to one skilled in the art to combine the references cited in the Office Action.

Accordingly, the Office Action fails to make a prima face case of obviousness as no proper combination of the cited references teaches or suggests the combination of steps claimed. Applicant respectfully requests withdrawal of the rejection of claims 1-3, 5, 7, and 9-14.

IV. Conclusion

Applicant respectfully submits the claims are in condition for formal allowance which is courteously solicited. If any issue regarding the allowability of any of the pending claims in the present application could be readily resolved, or if other action could be taken to further advance this application such as an Examiner's amendment, or if the Examiner should have any questions regarding the present amendment, it is respectfully requested that the Examiner please telephone Applicant's undersigned attorney in this regard. Should any fees be necessitated by this response, the Commissioner is hereby authorized to deduct such fees from Deposit Account No. 11-0160.

Applicants' request for extension of time under 37 C.F.R. § 1.136(a) as well as Applicants' petition fee are enclosed herewith and filed simultaneously with this response.

Respectfully submitted,

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